

Explainable AI Reveals Hidden Treatment-Responsive Subgroups in the A4 Solanezumab Trial

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RESEARCH QUESTION: Can an explainable AI-based approach that allows for discovery of synergistic variables identify clinically interpretable subpopulations with differential response to solanezumab in the Anti-Amyloid Treatment in Asymptomatic Alzheimer’s Disease (A4) Study?

METHODS

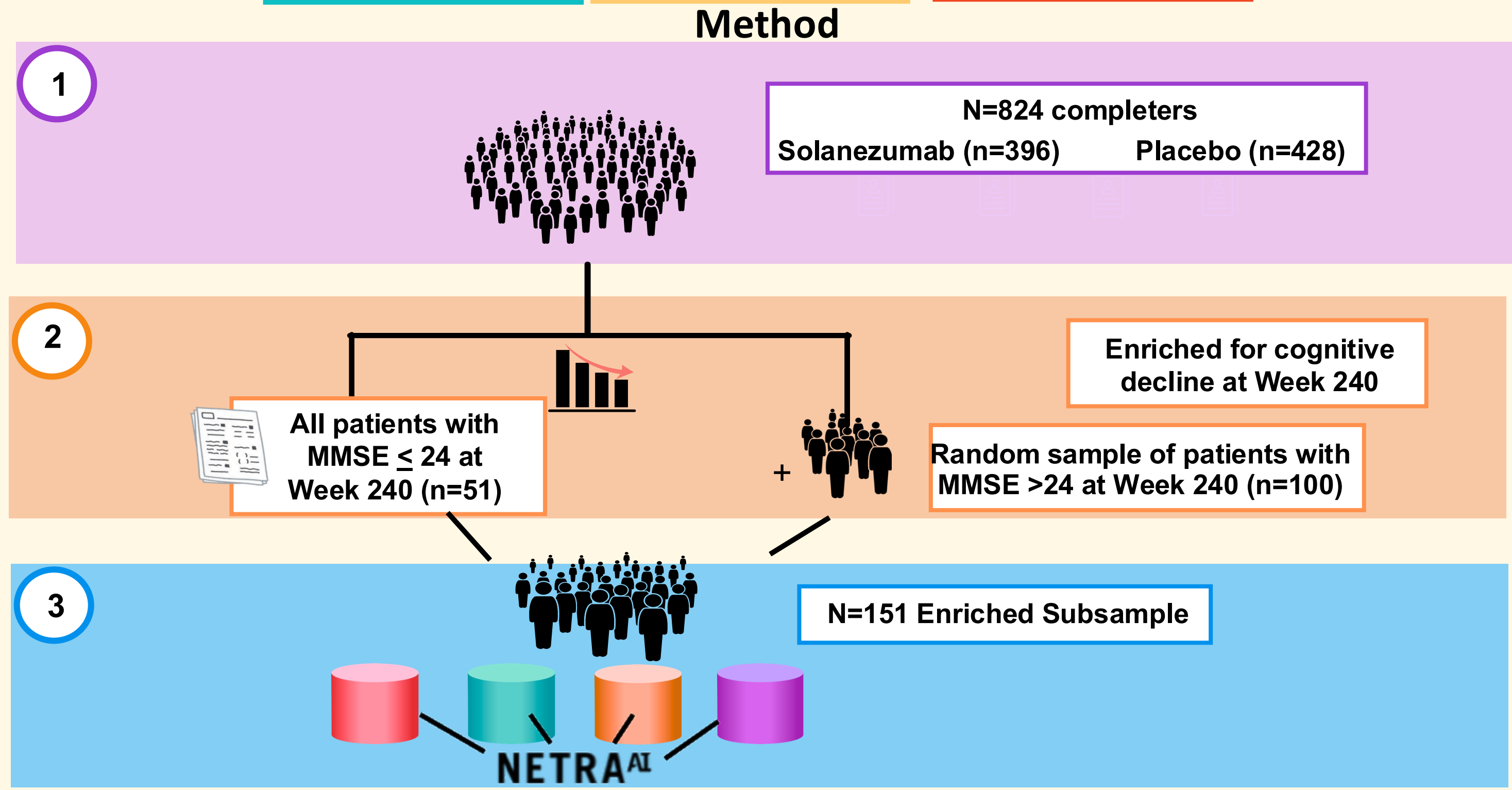
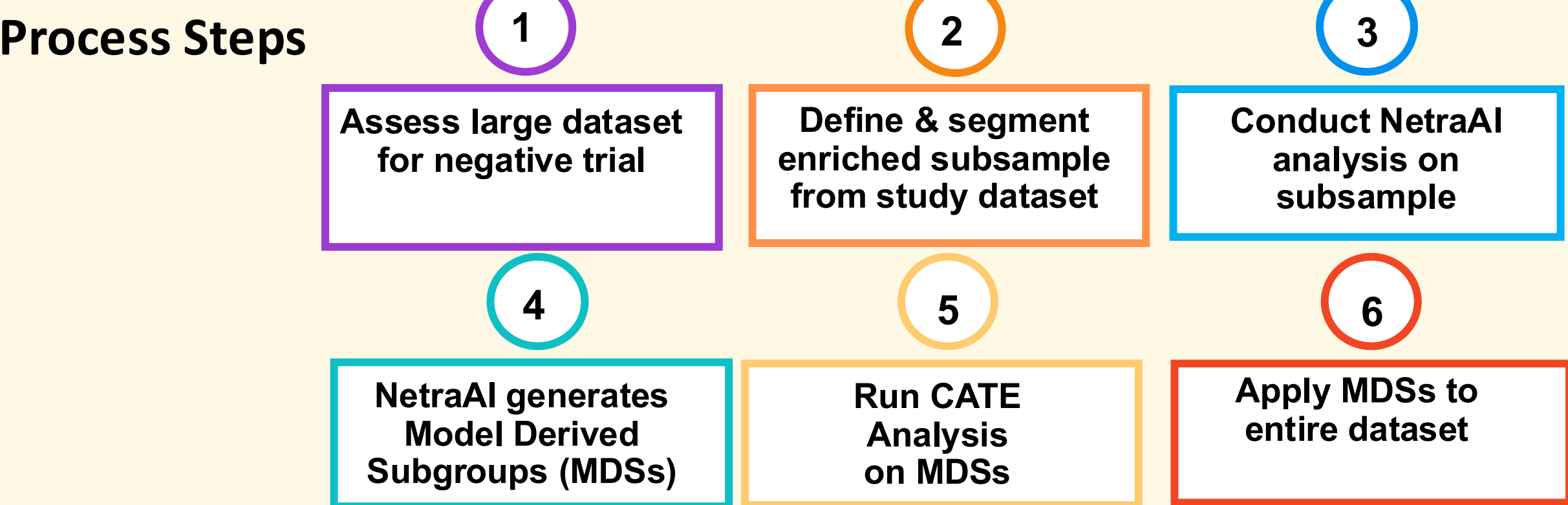
A novel attractor-based AI approach (Geraci et al., 2025) was applied to the A4 dataset of clinically asymptomatic older adults with elevated amyloid randomized to solanezumab (sola) or placebo.

Primary endpoint: Change in Preclinical Alzheimer Cognitive Composite (PACC) through Week 240

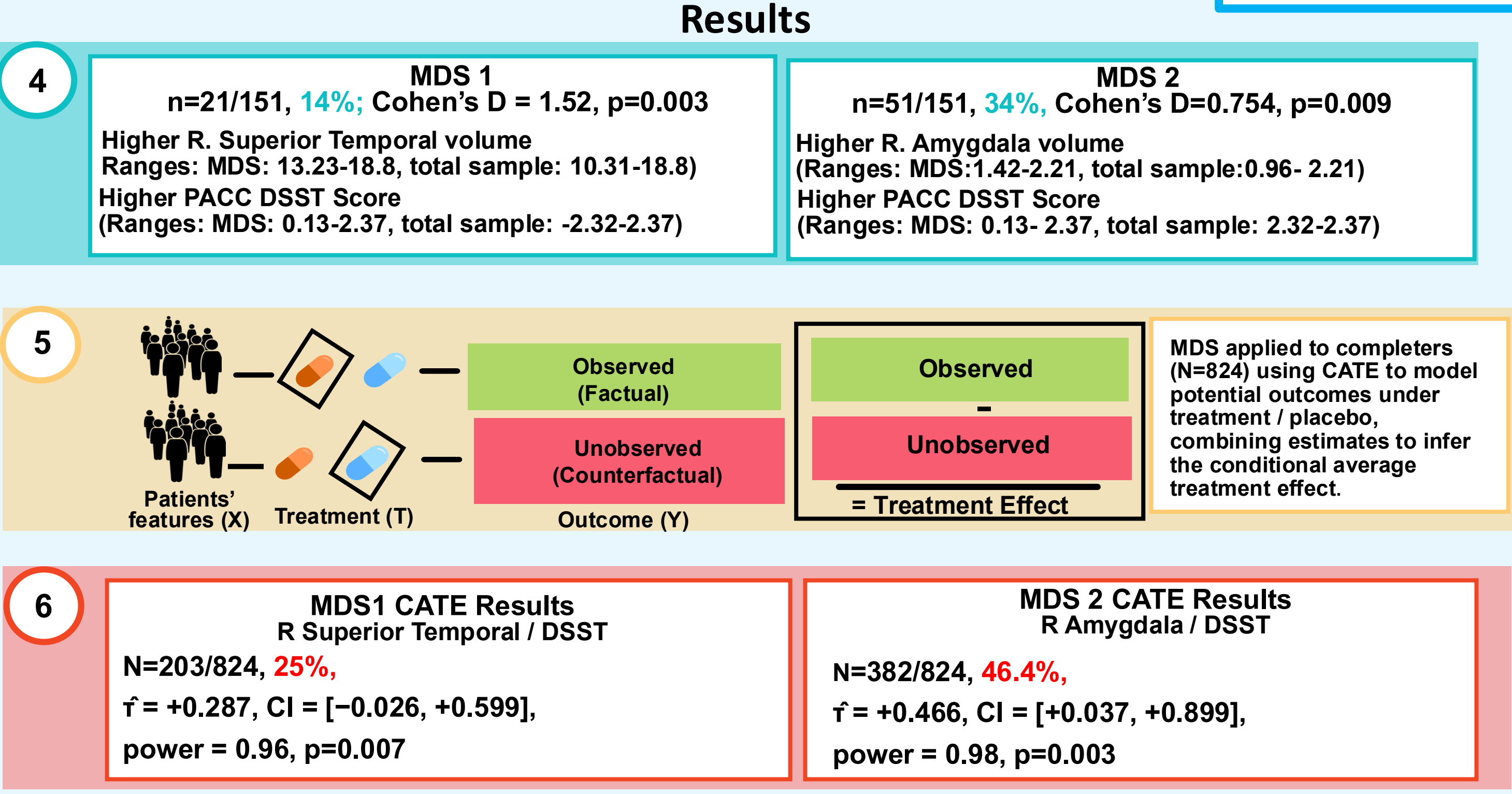
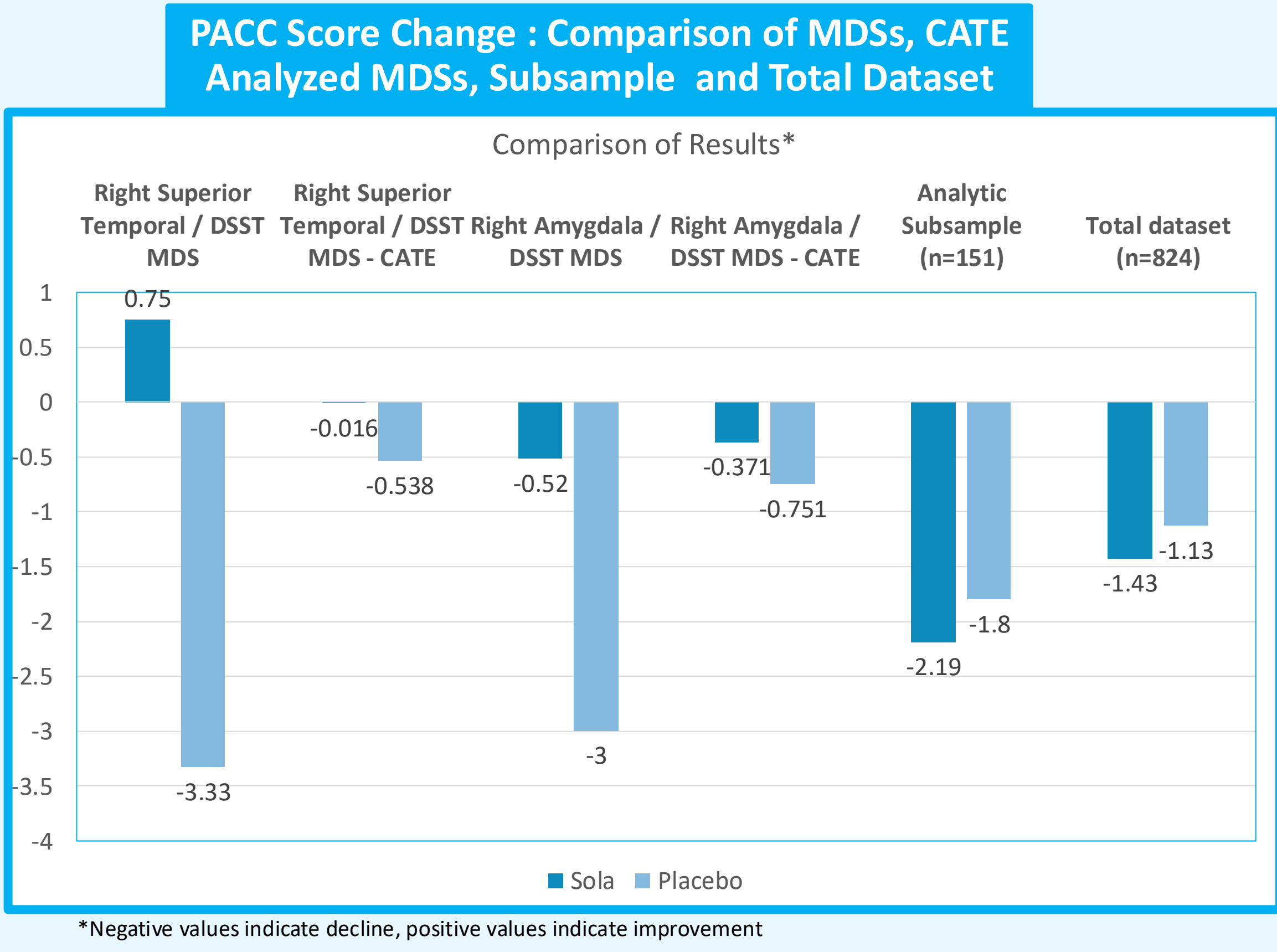
Population: Asymptomatic at baseline with minimal decline over time (average MMSE score 28.8 at Baseline to 28.5 at Week 240, Rentz et al., 2024). Due to lack of clinical change, we used an enriched subsample with all participants who progressed to MCI (n=51) and a matched unimpaired group (n=100).

NetraAI Subgroup Identification: Candidate subpopulations defined by 2–4 baseline features were identified based on stability, interpretability, and consistency of effect direction.

CATE Analysis: Subgroup definitions were then measured within the the full randomized cohort (n=824) using counterfactual causal inference to estimate conditional average treatment effects (CATE).



RESULTS



NetraAI Results:

2 subpopulations with greater regional brain volume + stronger baseline psychomotor speed / attention had less cognitive decline with sola at Week 240.

- MDS 1: **higher baseline r. superior temporal volume** + higher baseline PACC DSST
- MDS 2: **higher baseline r. amygdala volume** + higher baseline PACC DSST
- Both NetraAI-generated MDS replicated within the enriched subsample and again using CATE analysis. NetraAI analyses generated specific subgroups showing treatment response. CATE analyses estimated this result across the entire dataset.

Original A4 trial:
No significant benefit (Cohen's d = ~0, p=0.26). Explainable AI identified two subgroups with significant treatment effect.

INTERPRETATION, LIMITATIONS, CONCLUSIONS & REFERENCES

Interpretation: Explainable AI revealed biologically coherent responder profiles characterized by superior baseline limbic and temporal network structure and stronger baseline cognitive performance. This suggests that treatment response in preclinical AD may require preserved neural reserve. Failure of overall trials may mask meaningful subgroup benefit. Application of CATE Analysis generalized these findings to increase applicability.

Limitations: Small enriched discovery subgroup; internally cross-validated and bootstrap-stable findings; independent replication in an untouched trial required.

Conclusions: Brain and cognitive reserve found two treatment-responsive subgroups; 2) Cross-fitted causal validation supports frozen NetraAI MDS as prospective enrichment cohorts for testing in an independent preclinical AD trial.

References: Geraci J, Qorri B, Tsay M, Cumbaa C, Leonczyk, P, Alphs L, et al. Explainable AI-driven precision clinical trial enrichment: demonstration of the NetraAI platform with a phase II depression trial. *NPJ Digit Med.* 2025,8(1):749.

Rentz DM, Rosenberg PB, Sperling RA, Donohue MC, Raman R, Liu A, Aisen PS. Characterizing Clinical Progression in Cognitively Unimpaired Older Individuals with Brain Amyloid: Results from the A4 Study. *J Prev Alzheimers Dis.* 2024;11(4):814-822. doi: 10.14283/jpad.2024.123.

Ling Y, Upadhyaya P, Chen L, Jiang X, Kim Y. Emulate randomized clinical trials using heterogeneous treatment effect estimation for personalized treatments: Methodology review and benchmark. *J Biomed Inform.* 2023 Jan;137:104256. doi: 10.1016/j.jbi.2022.104256.

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DISCLOSURES

Dr. Joseph Geraci is the founder of NetraMark and is a significant shareholder of NetraMark Holdings, which is a publicly traded company. Luca Pani, Jan Sedway, Christian Cumbaa, Bessi Qorri, Mike Tsay, Paul Leonchyk, and Larry Alphs are employed by NetraMark. Dr. Luca Pani's Disclosures (past 3 years): Luca Pani has been a consultant or advisory board member for AbbVie, USA; BCG, Switzerland; Boehringer Ingelheim International GmbH, Germany; GH Research, Ireland; Immunogen, USA; Johnson & Johnson USA; LB Pharmaceuticals, USA; Magdalen Biosciences, USA; Sanofi-Aventis, Germany, France and USA; Lundbeck, Denmark and Italy; Nappo Pharma, USA and EU; NetraMark, Canada; Pfizer Global, USA; Reimada Therapeutics, USA; Takeda, USA and owns shares/options from AIDance Germany, Adapt UK, Enzeta USA, NetraMark Canada, and Reimada, USA.



SCAN ME

KEY FINDINGS

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- Explainable AI uncovered clinically interpretable responder subgroups within a negative Phase 3 trial
- Counterfactual causal inference was able to estimate conditional average treatment effects in entire dataset
- Subgroups with baseline levels of greater regional brain reserve (right amygdala / right superior temporal cortex) and stronger baseline psychomotor speed / attention were more responsive to solanezumab
- Treatment effect was large (power = 0.96-0.98 after CATE analysis) with minimal placebo-associated benefit
- Suggests anti-amyloid efficacy may depend on preserved network integrity